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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/742,454	12/19/2000	Steven R. Wiley	2968-B	8855

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EXAMINER	
YAEN, CHRISTOPHER H	
ART UNIT	**PAPER NUMBER**
1642	22

DATE MAILED: 12/16/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/742,454	WILEY, STEVEN R.	
	Examiner	Art Unit	
	Christopher H Yaen	1642	

-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *39 and 46-71* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *39 and 46-71* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *21* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 9/04/2003 has been entered.

2. Claims 1-38, 40-45, and 72-90 are canceled.

3. Claims 39, and 46-71 are pending and examined on the merits.

Information Disclosure Statement

4. The Information Disclosure Statement filed 9/4/2003 (paper no. 21) is acknowledged and considered. A signed copy of the IDS is attached hereto.

Specification

5. The disclosure is objected to because of the following informalities: on page 2, line 5, TWEAK R is disclosed as being a type II membrane protein where the C-terminal domain is the extracellular portion. However, on page 29, example 5, methods of evaluating the signaling events mediated by the cytoplamsic domain of TWEAKR via TRAF family members was accomplished via a 29 amino acid portion of the C-terminal

domain. Does the applicant intend to examine the 29 amino acids from the "N-terminal" domain?

Appropriate correction is required.

Claim Rejections - 35 USC § 112, 1st paragraph

6. Claims 39, 46-58, and 71 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The following *written description* rejection is set forth herein.

The claims recite a "TWEAK receptor antagonist" as part of the invention. However, there does not appear to be an adequate written description in the specification as-filed of the essential structural feature that provides the recited function of antagonizing a TWEAK receptor. The Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement make clear that the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the

applicant was in possession of the genus (Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001, see especially page 1106 3rd column).

Applicant does not appear to have reduced, with the exception of a TWEAKR-Fc fusion protein, a representative number of antagonists so as to be entitled to the broad genus of TWEAKR antagonists claimed. Neither has Applicant provided a sufficient written description of any structure, with the exception of TWEAKR-Fc, that may be correlated with the desired antagonistic function. A "TWEAK receptor antagonist" encompasses *any* molecule with the functional activity of blocking or interfering with the binding of TWEAK to the TWEAKR, thereby preventing or inhibiting the signaling caused by the said receptor in other down stream events. Such inhibition of downstream signaling events would thereby prevent diseases associated with angiogenic events. Thus the genus of compounds encompassed by this term is extensive and the artisan would not be able to recognize that Applicant was in possession of the invention as now claimed.

Consequently, Applicant was not in possession of the instant claimed invention. See Regents of the University of California v. Eli Lilly and Co. 119 F.3d 1559, 43 USPQ2d 1398 (Fed. Cir. 1997). Adequate written description of genetic material "'requires a precise definition, such as by structure, formula, chemical name, or physical properties,' not a mere wish or plan for obtaining the claimed chemical invention." Id. 43 USPQ2d at 1404 (quoting Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606). The disclosure must allow one skilled in the art to visualize or recognize the identity of the

subject matter of the claim. Id. 43 USPQ2d at 1406. A description of what the genetic material does, rather than of what it is, does not suffice. Id.

While it is noted that the instant claims are drawn to methods, the claims nevertheless require an adequate written description of the "TWEAK antagonist" employed in the methods.

Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

Claim Rejections - 35 USC § 112, 1st paragraph

7. Claim 71 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of inhibiting the binding of TWEAK to a TWEAKR in a mammal comprising the addition of an TWEAKR-Fc fusion protein or an antibody to TWEAKR wherein the inhibition is mediated by binding to the extracellular portion of the TWEAK R, does not reasonably provide enablement for a method of inhibiting the binding between a TWEAKR and TRAF family member. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claim is drawn to a method of inhibiting angiogenesis comprising the administration of an antagonist to TWEAKR wherein the antagonists disrupts the interaction between TWEAKR and TRAF.

The specification teaches the evaluation of TWEAKR and TRAF (example 5) by using a 29 amino acid portion from the C-terminal domain (see page 29). The specification teaches that TWEAK R is a type II membrane protein wherein the C-terminal end is the extracellular domain of the receptor (see page 2). The specification also teaches that the TRAF family are intracellular signaling molecules that are known to associate with TNF family members (see page 29).

The art teaches that TRAF Family members bind to play diverse roles in adaptive and innate immune responses, and that such interactions with the TNF receptor family mediates the major mechanism of signaling of the said receptor family (see Chung *et al* J Cell Sci. 2002 Feb 15;115(Pt 4):679-88). Therefore, it is unclear as to how one of skill in the art would be able to use the teachings of the specification in combination with the art of record at the time the invention was filed to practice the instantly claimed invention. It is unclear how a 29 amino acid span derived from the C-terminal domain or extracellular domain is to mediate signaling events of the TRAF intracellular protein. One of skill in the art would be forced into undue experimentation to practice the instantly claimed invention because it is clear that TRAF is an intracellular protein and that the C-terminal domain of TWEAKR is part of the extracellular portion, and that interactions between TRAF and TWEAKR extracellular domain are not disclosed in the specification nor disclosed in the art. One of skill in the art would be forced to determine how or if any such interaction between TRAF and TWEAKR extracellular domain exists.

Therefore, given the teachings of the art with regard to the interactions between TRAF and TNF receptor family members (of which include TWEAKR), the lack of

disclosure involving such molecule and TWEAK R, one of skill in the art would be forced into undue experimentation to practice the instantly claimed invention.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language

9. Claims 39 is rejected under 35 U.S.C. 102(e) as being anticipated by Rennert P (US Pre-Grant Publication 2002/0015703 A1, published 7 February 2002, IDS filed 9/4/2003). The claim is drawn to a method of inhibiting the binding of a TWEAK to a TWEAK receptor comprising the administration of a TWEAK receptor antagonist selected from the group consisting of a soluble TWEAK receptor polypeptide, an antibody that binds to TWEAK receptor, an anti-sense nucleic acid, a triple helix forming nucleic acid, a peptide, and a small molecule. Rennert P disclose a method of blocking the development or treating or reducing the severity of or effects of an immunological disorder comprising the administration of a tweak blocking agent, wherein the blocking

agent can be a soluble TWEAK receptor that binds to TWEAK, an monoclonal antibody that binds to TWEAK receptor, or an agent that modifies the cell surface receptor.

Claim Rejections - 35 USC § 103

10. Claims 39, and 46-70 are rejected under 35 U.S.C. 103(a) as being obvious over Rennert P. (cited above) in view of Lynch *et al* (IDS filed 5/11/2001) in further view of Miller AR (Surg Oncol Clin N. Am. 1998 Jan;7(1):183-197) and Parish (US Patent 5,677,181).

Claims are drawn to a method of inhibiting the binding of a TWEAK to a TWEAK receptor comprising the administration of a TWEAK receptor antagonist selected from the group consisting of a soluble TWEAK receptor polypeptide, an antibody that binds to TWEAK receptor, an anti-sense nucleic acid, a triple helix forming nucleic acid, a peptide, and a small molecule (claim 39). The claims are also drawn to a method of inhibiting angiogenesis comprising the administration of a TWEAK receptor antagonist (claim 46); wherein the composition further comprises a pharmaceutical carrier (claim 47); wherein the mammal is human (claim 48), wherein the mammal has a disease or condition mediated by angiogenesis (claim 49, 62), wherein the disease or condition is characterized by ocular neovascularization (claim 50, 63), wherein the disease or condition is a malignat or metastatic condition (claim 51, 64), wherein the malignant or metastatic condition is a solid tumor (claim 52, 65); wherein the method further comprises treatment with radiation (claim 53, 66); wherein the method further comprises treatment with a chemotherapeutic agent (claims 54-57, 67-70); wherein the TWEAK

receptor antagonist is selected from the group consisting of a soluble TWEAK receptor polypeptide, an antibody that binds to TWEAK receptor, an anti-sense nucleic acid, a triple helix forming nucleic acid, a peptide, and a small molecule (claim 58), wherein the antagonist comprises an antibody that binds to the TWEAK receptor extracellar domain (claim 59), wherein the antibody is monoclonal, humanized, transgenic, or human (claim 60), and wherein the antibody is conjugated to a radioisotope, plant/fugus/bacterial derived toxin, ricin A, DT, or a chemical poison (claim 61).

Rennert P (see above paragraph 7 for Rennert P disclosure) does not specifically characterize a method of using the TWEAK receptor antagonist for a method of treating angiogenesis or angiogenesis related diseases such as cancer or ocular neovascularization. Rennert P also does not characterize a method of using chemotherapy or radiation or using antibody conjugates in conjunction with the TWEAK receptor antagonists. These deficiencies are made-up by Lynch *et al*, Miller A *et al*, and Parish.

Lynch *et al* disclose the role of TWEAK (and indirectly TWEAK receptor) in angiogenesis, wherein it was disclosed that TWEAK was involved in the induction of angiogenesis.

Miller A *et al* taught that the combination of chemotherapeutic and radiation therapy could be combined with low-toxicity treatments such as inhibitors of angiogenesis (see abstract). And finally, Parish taught that antibodies used the inhibition of angiogenesis could be conjugated with radioisotopes.

Therefore, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use TWEAK receptor antagonist for the treatment of angiogenesis, and to further combine methods of chemotherapy or radiation therapy with the methods of using TWEAK receptor antagonists for the treatment of angiogenesis and angiogenesis related disorders. One of ordinary skill in the art would have been motivated to do so because Rennert P taught methods of using TWEAK receptor antagonists for the treatment of TWEAK related diseases and disorders and Lynch *et al* taught the relationship between the TWEAK and its role in inducing angiogenesis. One of ordinary skill in the art would have realized that inhibition of angiogenesis through the antagonization of the TWEAK receptor would be a reasonable means of inhibiting angiogenesis. Furthermore, because it is well known and taught in the art that angiogenesis is associated with cancer and the growth of cancer, other methods could be combined with the angiogenesis inhibition, such as chemotherapy and or radiation therapy. Because Miller *et al* taught that inhibitors of angiogenesis could be combined with a method of chemoradiation, to generate a more potent form of cancer treatment, one of skill in the art would have expected a reasonable amount of success in combining the method of antagonizing TWEAK receptor with chemotherapy and or radiation therapy. And finally, the skilled artisan would have had reasonable success in conjugating an isotope or any other molecule to a TWEAK antagonizing antibody for the treatment of angiogenesis because Parish *et al* taught that antibodies conjugated to radioisotopes where effective in reducing angiogenesis.

Therefore, given the basic teachings of Rennert P in using TWEAK receptor antagonist for the reduction of diseases associated with TWEAK receptor, the fact that TWEAK and it receptor are involved in angiogenesis, one of skill would have found it obvious to use the antagonists of Rennert P in methods of treating angiogenesis in conjunction with chemotherapy/radiation or with radioisotope conjugated antibodies.

Conclusion

11. Claims 39, 46-71 are rejected.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher H Yaen whose telephone number is 703-305-3586. The examiner can normally be reached on Monday-Friday 9-5.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone number for the organization where this application or proceeding is assigned is 703-308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Christopher Yaen
Art Unit 1642
December 8, 2003